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## Unmodifiable variables related to thyroid cancer incidence

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## **Cover Page Footnote**

All authors contributed equally.

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## Research article

# Unmodifiable variables related to thyroid cancer incidence

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### Abstract

The incidence of thyroid cancer is significantly different between male and female patients. Thyroid cancer is also the only form of cancer where age can be considered a staging variable. Identifying biological prognostic factors such as age or sex is important as it helps select an optimal personalized therapy. The present analysis is an observational, prospective study that enrolled all patients with thyroid disease who were operated upon at a single center. The study aimed to determine the most frequent age at presentation, the predominance of one sex over the other, the incidence of malignant thyroid disease, and the relative risk for each sex to develop thyroid carcinoma. The incidence of thyroid carcinoma was higher for women than for men, with a higher relative risk in the female subgroup. Incidence was also highest in the 50-60-year-old group. Given that studies show better survival for women and for younger patients, even when presenting with advanced disease, compared with older, male patients, such prognostic indicators should be a factor in the treatment decision.

### Keywords

: thyroid cancer, age, gender, prognosis, total thyroidectomy

### Highlights

- ✓ The incidence of thyroid carcinoma seems to be higher for women than for men,
- ✓ Women and for younger patients present better survival, even when they present with advanced disease, as compared with older, male patients.
- ✓ Such prognostic indicators should be considered important factors in the therapeutic decision

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## Introduction

Significant variation in the incidence of thyroid cancer among women and men has long led to speculation about the possible biological theories underlying the development and progression of this disease. The annual percentage of thyroid malignancies for both women and men increased between 1980 and 1997 by 2.4% per year, and by 6.6% per year between 1997 and 2009 (1). This increase does not necessarily reflect a higher incidence, but only the possible expansion of screening techniques that provide easier access for diagnosis.

Thyroid cancer is the most common malignant disease of the endocrine system and the 7th most common neoplasia in women, although in the case of men, it is not among the 15 most frequent cancers (2). Thyroid cancer is the only form of cancer where age can be considered a staging variable (3). This study attempted to identify whether a link exists between age and sex of the patient and the risk of developing a certain type of thyroid cancer, while taking into account these two unchangeable variables. Identifying prognostic factors such as age or sex is important as it helps in determining an optimal personalized therapy instead of deciding treatment strictly based on the underlying disease.

## Materials and methods

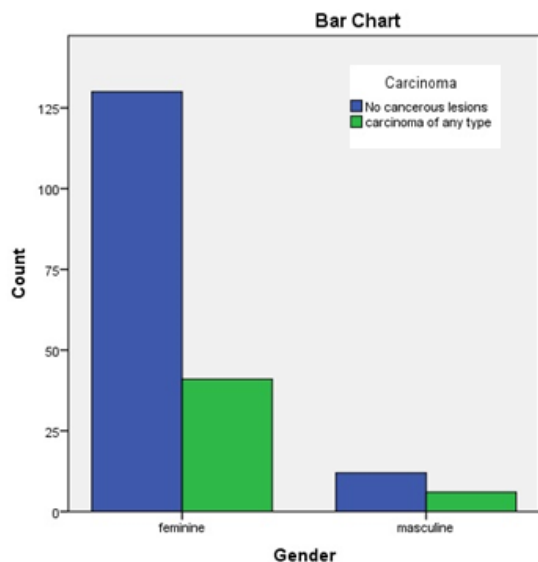
This observational, prospective study enrolled all patients with thyroid disease who were operated upon between January 2015 to January 2018 in the Clinic of General Surgery of the Emergency Clinical Hospital "Prof. Dr. Agrippa Ionescu," Bucharest, Romania, irrespective of the operative indication which included: symptomatic thyroid masses and goiter, refractory Graves disease or hyperthyroidism, or biopsy-proven thyroid cancer or solitary nodules with malignant characteristics on ultrasound. Exposure to prior radiation was an exclusion criterion. After completing the surgery, data regarding the patient's age, gender, and pathology report were collected. SPSS Statistics version 20 was used for data analysis. The ethics committee approved data collection for this research. All patients signed an informed consent and agreed to the usage of the data.

## Results

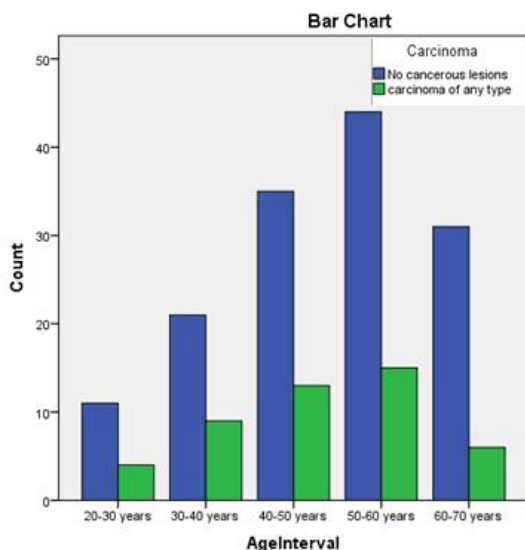
A total of 189 patients were included in the study. Of these, 171 (90.47%) were women and 18 (9.53%) were men. All patients underwent total thyroidectomy. Mean age of the entire group was 48,94 (minimum, 21; maximum 69, SD = 12,7). Mean age of the male group was 48.61 (minimum, 33; maximum, 69; SD =11.63), whereas for women the mean age was 48,84 (minimum, 21; maximum, 69). Of the women, 76% (n=130) had no cancerous lesion on the thyroidectomy pathology report, while 24% (n=41) tested positive for cancer. Clinicopathologic characteristics of these patients are presented in Table 1.

| Variable          |            | Nr. | Percentage % |
|-------------------|------------|-----|--------------|
| Sex               | m          | 7   | 14,58%       |
|                   | f          | 41  | 85,41%       |
| Age (years)       | 21-30      | 4   | 8,33%        |
|                   | 31-40      | 9   | 18,75%       |
|                   | 41-50      | 14  | 29,16%       |
|                   | 51-60      | 16  | 33,3%        |
|                   | 61-70      | 10  | 20,83%       |
| Histology         | papillary  | 45  | 93,75%       |
|                   | follicular | 3   | 6,25%        |
|                   | medular    | 1   | 2%           |
|                   | anaplastic | 1   | 2%           |
| Multifocality     |            | 10  | 20,83%       |
| Capsular invasion |            | 7   | 14,58%       |

Among men, 33.3% (n=6) had thyroid carcinoma and 66.7% (n=12) were free of neoplastic disease on pathology evaluation. The relative risk for malignancy among women was 1.140 (95% CI 0.56-4.49), OR 1.140 (95% CI 0.81-1.59). Among men, the relative risk for malignancy was 0.409 (95% CI 0.4-0.86), OR 0.75 (95% CI 0.5-1.1). The incidence of thyroid cancer in the two sexes was higher in women (Figure 1). Female to male ratio in the thyroid carcinoma subgroup was 3.23:0.90. The most frequent histologic subtype was papillary thyroid cancer (see Figure 1 for the carcinoma incidence by sex and age group).



**Figure 1.** Graphic representation of the carcinoma incidence for each gender



**Figure 2.** Graphic representation of the carcinoma incidence for each age subgroup

Patients were classified into 5 age groups in order to establish incidence rates. 7.9% (n=15) of the patients were 20-30 years old, 15.8% (n=30) were 30-40, 25.38% (n=48) were 40-50, 31.21% (n=59) were 50-60, and 19.57% (n=37) were 60-70. Of these, in the most representative group (50-60) 74.6% (n=44) were positive for cancer (Figure 2). Patients were thus divided into two subgroups: patients under 40 years, 51.32% (n=97), and patients over 40, 48.68% (n= 92). Relative risk for thyroid malignancy was 0.6 (95% CI 0.32-1.25) in the under 40 subgroup, OR= 0.89 (0.76-1.05) .

## Discussion

Identification of prognostic factors such as age and sex allow the patient to be classified epidemiologically and offers an optimal path of treatment. Even if the

prognosis of well-differentiated thyroid carcinomas as localized disease is excellent, in cases of regional disease or remote metastasis, survival may be influenced by age (4). In this sample, females had higher percentages among those who were both diagnosed and operated for various thyroid pathologies. The most frequent operative indication was polinodular goiter. Among objective criteria, hormonal activity and their oscillation both during the menstrual cycle and during pregnancy seem to positively influence this increased incidence. The peak incidence of thyroid cancer in the female subgroup occurred in the 50-60-year age group, this being the age most women become menopausal. Similar results have been reported elsewhere (5). However, the impact of hormonal oscillations cannot be clearly quantified; data collected by Negri et al. did not reveal a statistically significant link between reproductive factors and the incidence of thyroid cancer (6). Among potential risk factors, late menstruation, late delivery of the first child, surgically or medication-induced menopause, and abortion were listed. Truong et al. also identified an association between menopausal status and an increased incidence of thyroid cancer (7).

The peak incidence for thyroid carcinoma in men is reached at 60-69 years. The incidence rate between the two sexes is reported in the literature to be almost identical among 80-year-olds. (4). In our study, it was difficult to establish age subgroups having the most similar incidence, given the fact that women greatly outnumbered men. The related sex difference in incidence, aggressiveness, and prognosis of neoplasms has been observed for a variety of cancers. In sex-specific organs such as the uterus, prostate, ovary, and breast, this difference can easily be explained. However, some localizations found in both sexes, such as the thyroid, lung and liver also indicate clear sex differences in incidence and/or survival (2, 4, 8, 9).

Women have malignancy onset at a lower age, but men often have a more aggressive or advanced form at the time of diagnosis. The Age, Metastasis, Size and Size (AMES) criteria, which classify patients with low or high risk based on age, metastasis, tumour invasion, and tumour size, takes into account sex differences in patient risk stratification. The age limit at which patients without distant metastases are considered at high risk and, therefore, the less favorable prognosis, is 10 years lower for men (41 years) compared to women (51 years) (10). Other systems that use sex as a variable in staging include the European Organization for the Study and Treatment of Cancer and the gender, age and grade classification (11).

The role of sex hormones, which is well documented in both breast and prostate cancer, warrants mentioning. The function of these hormones is mediated through cellular nuclear receptors that can activate or inactivate certain genes having the potential to influence the biology of the tumour (12). Nuclear receptors of estrogen (alpha and beta estrogens) are well expressed in thyroid cancer, especially in the papillary forms which, as we observed in our study, was frequently encountered; with a total of 45 of 48 cases, 43 were identified in the female subgroup (13).

The prospective cohort study conducted by Iribarren et al. in 2001 on 204,964 people reported a relative risk for women to develop thyroid cancer of 1.56 (14). Our study reported a lower relative risk, probably because our sample size was lower, and the age of our sample was both lower and did not include as many 50-60-year-old women. Although more common in women, thyroid cancer in men has a more aggressive progression with a worse prognosis. Kruijff and colleagues have shown that the risk of recurrence is 2.44 times higher in men than in women at a median follow-up period of 31 months (14, 15).

As we have seen in our study, only 7 cases of thyroid cancer were seen in men, and two of these had an aggressive form: 1 case was anaplastic, 1 medullary case. Also, regarding staging, 4 of them were classified as advanced T3-T4 stages according to TNM.

Liu, in a recent article evaluating the prognostic role of the male sex in thyroid cancer, has confirmed its association with an increased risk of death, but this association disappears when adjustments are made for age, multifocality, and treatment received (16). Although current studies suggest that complete surgical resection and adjuvant radiotherapy is the standard of care, such factors as age, sex, and clinical-pathological parameters such as superior tumour grade (III / IV) and stage of cancer should be considered when assessing the risk of mortality in differentiated thyroid tumours (17). Unfortunately, the details of surgical therapies and radiotherapy were incomplete in the use of the survival analysis database. Further research is needed to discover the source of sex differences, implying interrelated (genomic and epidemiological) investigative studies, rather than the competitiveness between the various research groups (18). However, given the aggressive features and poor prognosis associated with aging, up-front adequate surgery should not be excluded from other therapeutic options in the elderly. It is known that increasing age negatively affects the prognosis of

thyroid cancer, and thus previous studies have used various ages as cutoff points for prognostic value (19).

Papillary thyroid carcinoma is the most frequently encountered type of carcinoma reported in patients positive for malignancy and is known for its good prognosis regarding survival. However, some histological subtypes, like the tall cell variant for example, do not warrant such an optimistic prognosis (20). Other aggressive histological subtypes like medullary carcinoma are very often part of a genetically inherited syndrome, such as MEN (multiple endocrine neoplasias), and do not follow the incidence pattern of more frequent ones (21).

Gilliland et al. and later, Hundahl et al. both demonstrated that the patient's age at presentation is an independent factor associated with survival, so young patients diagnosed with an advanced stage disease have a better survival than the elderly with an early stage disease. The explanation for this pattern is still unknown (22-24). In our study, mean age of the patients was nearly identical in the two subgroups.

Some retrospective trials have suggested that young adults present with advanced stage more often and have more frequent recurrences than patients over 65.5 years old. Even so, paradoxically, overall survival is superior in the young patient subgroup (25, 26).

## Conclusions

Women present more often with thyroid disease for which surgery is mandatory. Age at presentation was similar in this study for both men and women. The incidence of thyroid carcinoma was higher for women than for men, with a higher relative risk in the female subgroup. Incidence of malignancy was highest in the 50-60-year-old group. Given that studies show better survival for women and for younger patients, even when they present with advanced disease, as compared with older, male patients, prognosis should be considered a relevant factor in the treatment decision. Further research is needed to better understand the prognostic significance of age and gender.

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